FORMATION OF 3,3-DISUBSTITUTED INDOLENINES FROM INTRAMOLECULAR NITRENE REACTION WITH ISOQUINOLINE AND NAPHTHALENE MOIETIES[1]

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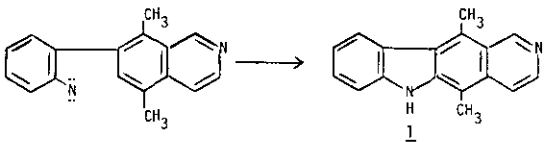
Abstract — Thermolysis of azides 2,7, and 14 gave nitrenes which reacted intramolecularly with isoquinoline and naphthalene moieties to produce 3,3-disubstituted indolenines 3,8, and 15, respectively, as the major products and carbazole derivatives 1,9, and 16, respectively, as the minor products.

In a program to develop synthetic approaches[2,3] to ellipticine (1), a 6H-pyrido[4,3-b]-carbazole alkaloid possessing significant anticancer activity,[4] we decided to investigate a nitrene insertion route:



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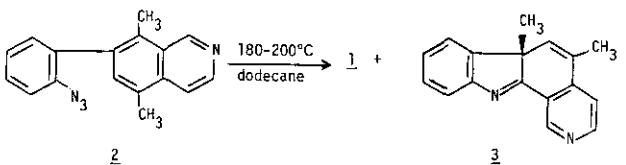
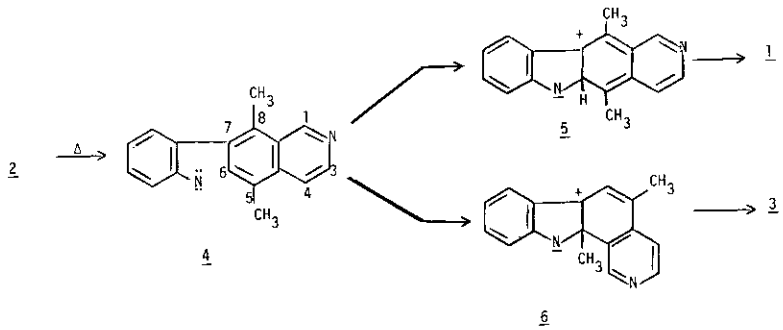
The azido compound 2[5] was chosen as the nitrene precursor and upon heating (180-200°C) in dodecane gave two isolable products. The minor product (20% yield) was identified as ellipticine by comparison with an authentic sample[2]. The major product (60% yield) displayed in its nmr spectrum an upfield methyl signal (δ=1.41, s), a vinylic methyl signal (δ=2.09, d,J=1.5Hz) and a vinylic proton signal (δ=6.53, q, J=1.5Hz) all of which indicated that the ring bearing the methyl groups was no longer aromatic. The structure of this compound was shown to be the 3,3-disubstituted indolenine 3 by single crystal X-ray structure analysis.[6] The partitioning of the reaction pathway between



2 1 + 3

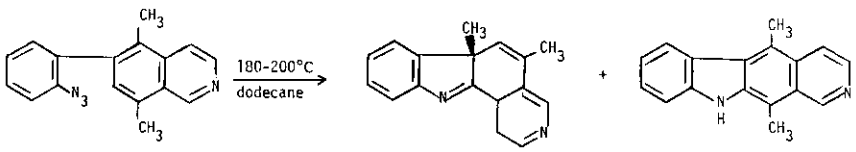
1 and 3 is rationalized by the routes shown in Scheme I. Thus thermolysis of azide 2 forms the electron deficient nitrene 4 which can react with the isoquinoline moiety at either position C-6 or C-8. Attack at C-6 would lead to intermediate 5 and, following proton shift, give rise to ellipticine (1). Attack at C-8 would lead to intermediate 6 and, following methyl migration to the electron deficient site, give rise to indolenine 3.

Scheme I

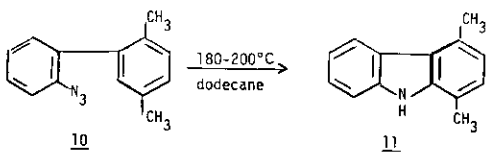


A comparison of electron densities and reactivities toward electrophilic attack at various positions in the homonuclear ring of isoquinoline shows an order of C-5 > C-8 > C-7 > C-6.[7] Thus the observation that compounds 1 and 3 are formed in a 1:3 ratio is consistent with the partitioning of the reaction pathways based upon the preferred site for electrophilic attack.

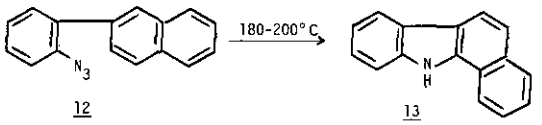
If this were the case, one would predict a similar mixture of products upon thermolysis of azide 7. Here the choice of attack of the nitrene is C-5 versus C-7. Attack at C-5 would give indolenine 8, while attack at C-7 would give isoellipticine (9). When azide 7[8] was heated (180-200°C) in dodecane a 3:1 ratio of 8[8] to 9[9] was obtained.



To investigate the influence of the methyl group at the site of attack, several studies were carried out. First, the biphenyl azide 10 was thermolyzed and gave only one product, 1,4-dimethylcarbazole(11)[8]. No 3,3-disubstituted indolenine was either isolated or detected in the nmr

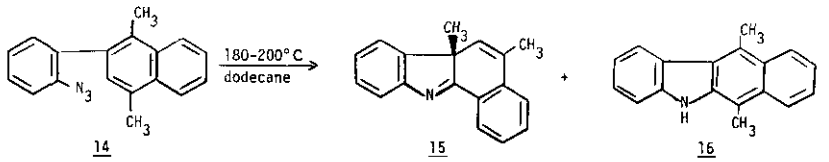


spectrum of the crude reaction mixture. This observation indicates that the nitrene would prefer to attack a C-H site relative to a C-CH_3 site if other reactivity factors are equivalent. This point is further emphasized by comparing the thermolysis of 2-(2'-azidophenyl)naphthalene(12) and 2-(2'-azidophenyl)-1,4-dimethylnaphthalene(14). Since the C-1 position of naphthalene is known to be more reactive than C-2 toward electrophilic attack,[10] it is consistent that Smith[11] observed that heating (180-200°C) 12 in kerosine gave 1,2-benzocarbazole(13) in 94% yield; attack at C-2 leading to 2,3-benzocarbazole "did not occur to a detectable extent." However, when azide 14[8] was



12 13

heated (180-200°C) in dodecane a 3:1 ratio of indolenine 15[8] and carbazole 16[9] was obtained. Thus it is clear that the presence of the methyl group at the C-1 position in 14 decreases the reactivity



14 15 16

at this site and makes attack at C-2 become competitive. Since the ratios of indolenine to carbazole are similar, this would appear to also be the case with azides 2 and 7.

ACKNOWLEDGEMENTS

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FOOTNOTES AND REFERENCES

1. This paper is warmly dedicated to Professor Gilbert Stork on the occasion of his 65th birthday.
2. For earlier approaches from our laboratories, see: R. B. Miller and J. G. Stowell, J. Org. Chem., 1983, 48, 886; R. B. Miller and T. Moock, Tetrahedron Lett., 1980, 21, 3319.
3. For recent approaches from other laboratories, see: G. W. Gribble, M. Saulnier, M. P. Sibi, and J. A. Obaza-Nutaitis, J. Org. Chem., 1984, 49, 4518 and references cited therein.
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6. The single crystal X-ray crystallographic data will be published elsewhere.

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